polymeric forms or their combinations and adenosine derivatives in a physiologically and pharmaceutically acceptable carrier, optionally with one or more excipients.

The methods involve the co-administration of an effective amount of Nicotine, nicotinic acid, polymeric forms or their combinations and an effective amount of an apomorphine, adenosine and / or NO donor in low, daily dosages for a week or more. One or both components can be delivered locally via catheter. Nicotine, nicotinic acid, polymeric forms or their combinations can be delivered to capillary beds surrounding ischemic tissue by incorporation of the compounds in an appropriately sized liposome or microparticle. Nicotine, nicotinic acid, polymeric forms or their combinations can be targeted to ischemic tissue by covalent linkage with a suitable antibody.

The method may be used as a treatment to restore cardiac function after a myocardial infarction. The method may also be used to improve blood flow in patients with coronary artery disease suffering from myocardial ischemia or inadequate blood flow to areas other than the heart, for example, occlusive peripheral vascular disease (also known as peripheral arterial occlusive disease), where decreased blood flow is a problem.

CLAIMS

What is claimed is:

1. A method for treatment of occlusive vascular diseases comprising of the administration of Nicotine, Nicotinic acid, and derivatives alone or in combinations.

2. A method for treatment of occlusive vascular diseases comprising of the administration of Polymeric forms of Nicotine, Nicotinic acid, and derivatives alone or in combinations.

3. A method of administering Claims 1-2 in combinations with Pro-angiogenesis factors such as fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF, and other pro-angiogenesis factors known in the art

4. A method of administering Claims 1-2 in combinations with vasodilators such as Nitric oxide donors, adenosine analogs, phosphodiaesterase inhibitors, apomorphine, and other vasodilators known in the art.

5. The method of Claims 1-4, wherein the disease to be treated is associated with occlusion of coronary, carotid or peripheral vessels.

6. The method of Claims 1-4, wherein the treatment involves the promotion of coronary, peripheral or carotid angiogenesis.

7. The method of Claim 2 wherein the Nicotine or its polymeric form is administered as a bolus injection prior or Post- administering oral Nicotinic acid daily for several weeks. Oral Nicotine or Intravenous polymeric forms of it could be administered daily for several weeks as well in conjunction with oral sustained release Nicotinic acid.

8. Compositions in Claims 1-4, to be used topically or systemically in impotence or erectable dysfunction. This would be of value in enhancing the effects of other standard therapies such as PDE 5 inhibitors including: Viagra. Viagra, Levitra, Cialis, other vasodilators or pro-angiogenesis agents such as VEGF, FGF2, and others.

9. The method of Claim 1-4, wherein the Nicotinic acid or nicotine, and derivatives are encapsulated or incorporated in a microparticle or liposome or polymers.

10. The method of claim 8 wherein the liposome or microparticle has a size less than 200 nm, and the liposome or microparticle is administered intravenously to the patient, permitting the liposome or microparticle to lodge in capillary beds.

11. The method of Claim 1-4, wherein the nicotinic acid or nicotine, and derivatives are administered via catheter.

12. The method of Claim 1-4, wherein the Nicotinic acid or nicotine, and derivatives are present in a polymeric system applied to the inside of a blood vessel via the catheter.

13. A pharmaceutical formulation for Claims 1-4, comprising Nicotinic acid or nicotine, and derivatives in a pharmaceutically acceptable carrier and salt form.

14. The pharmaceutical formulation of claim 1-4, additionally comprising one or more pharmaceutically acceptable excipients.

15. The pharmaceutical formulation of Claims 1-4, wherein the Nicotinic acid or nicotine, and derivatives are encapsulated or incorporated in a liposome or microparticle.

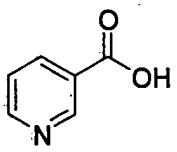
16. The pharmaceutical formulation of Claims 1-4, wherein the Nicotinic acid or nicotine, and derivatives are used in conjunction with vasodilators such adenosine and adenosine derivatives, and other standard vasodilators.

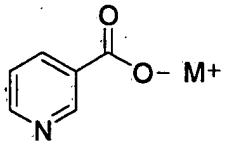
17. The pharmaceutical formulation of Claims 1-4, wherein the Nicotinic acid or nicotine, and derivatives are used in conjunction with anticoagulants such as heparin, heparin derivatives, anti-factor Xa, anti-thrombin, and other antithrombotics such as aspirin or clopidgrel.

18. Compositions in Claims 1-4, to be used topically or systemically in impotence or erectable dysfunction. Would be of value in enhancing the effects of other standard therapies such as PDE 5 inhibitors including: Viagra. Viagra, Levitra, Cialis, other vasodilators or pro-angiogenesis agents such as VEGF, FGF2, and others.

Nicotinic acid derivatives

Nicotinic acid or niacin is 3-pyridinecarboxylic acid.

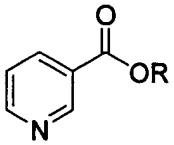




M = metals - sodium. potassium, etc. or ammonium salt

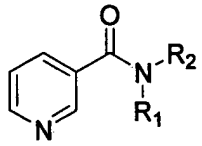
Using Scifinder, there are 11 hits when crossing this molecule with angiogenesis. Most of these incorporate it as a salt, salt derivatives such as amine carboxylates. Simple derivatives of the carboxylic acid are known compounds.

1. **Esters**, where R = alkyl, aryl, polymer and substituted variants thereof.



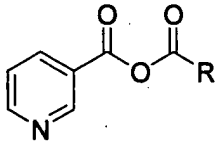
Esters are known to undergo hydrolysis *in vivo* to give the carboxylate.

2. **Amides**, R_1 or R_2 = hydrogen, alkyl, aryl, polymer and substituted variants thereof.



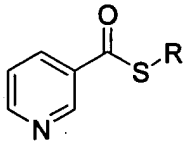
Amides are less likely to undergo hydrolysis *in vivo* than the esters.

3. **Anhydrides**, where R = alkyl, aryl, polymer and substituted variants thereof.



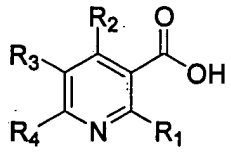
Anhydrides are typically very reactive in water and hydrolyze to the carboxylate rapidly.

4. **Thioesters**, where R = alkyl, aryl, polymer and substituted variants thereof.

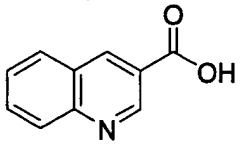


In general, thioesters are less susceptible towards hydrolysis than esters.

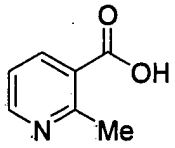
5. **Ring derivatives**, where R1 – R4 = alkyl, aryl, polymer, halides, ethers, etc. and substituted variants thereof.



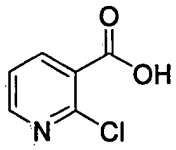
Some examples include,



3-quinolinecarboxylic acid



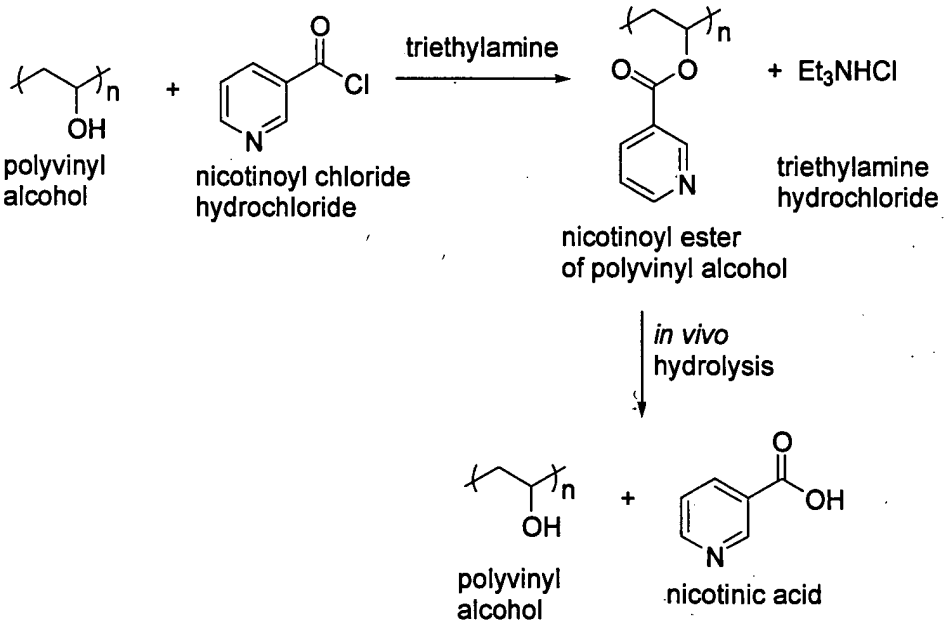
2-methyl-3-nicotinic acid



2-chloro-3-nicotinic acid

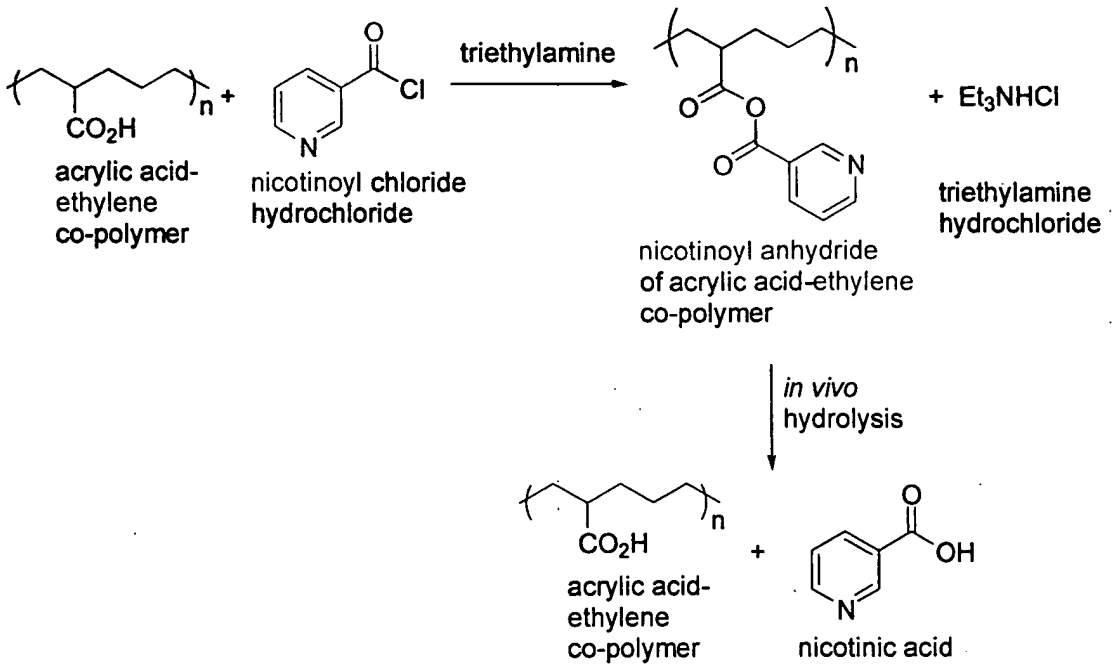
Below are three approaches to polymer systems for the *in vivo* release of 3-nicotinic acid.

1. Polymer conjugation through an ester linkage. Polyvinyl alcohol can be covalently conjugated to 3-nicotinic acid by reaction of the acid chloride of 3-nicotinic acid with polyvinyl alcohol.

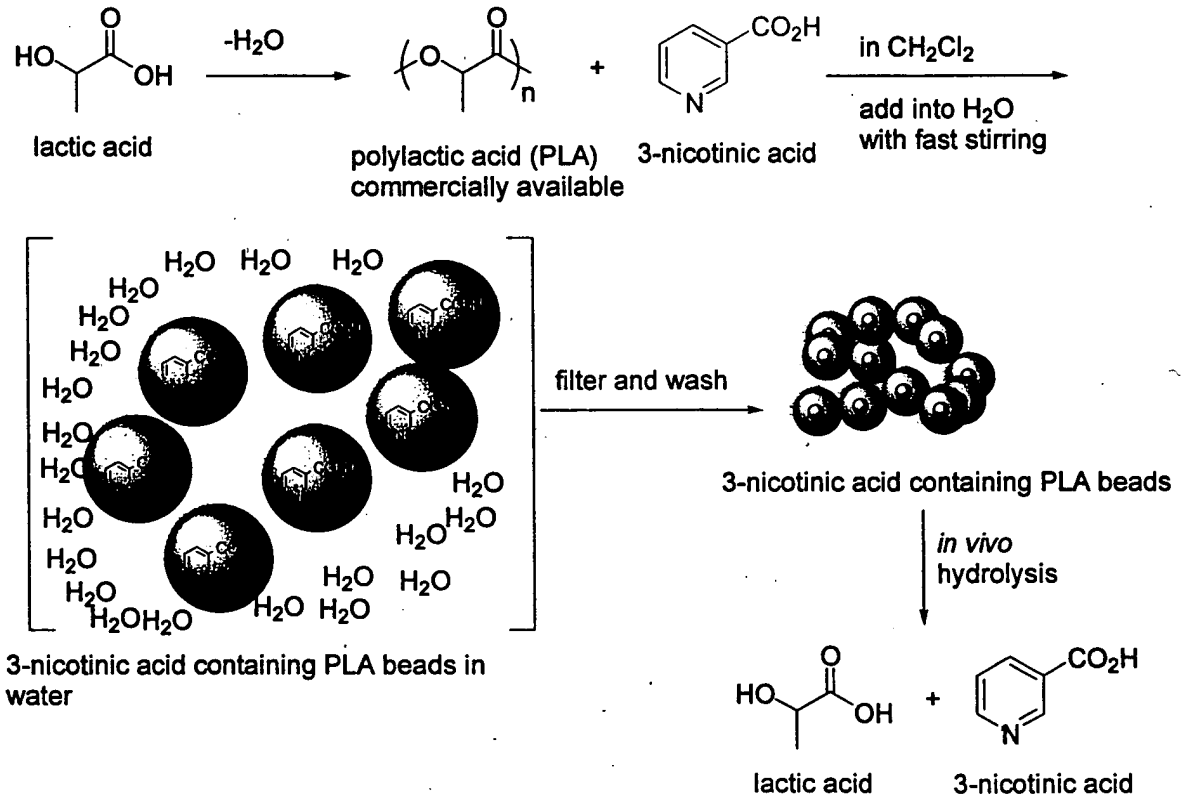


In this preparation commercially available polyvinyl alcohol (or related co-polymers) can be esterified by treatment with the acid chloride of 3-nicotinic acid, namely nicotinoyl chloride, which is commercially available as its hydrochloride salt. The hydrochloride salt is neutralized by the addition of triethylamine to afford triethylamine hydrochloride which can be washed away with water upon precipitation of the nicotinoyl ester polymer. The ester linkage to the polymer may undergo hydrolysis *in vivo* to release 3-nicotinic acid.

2. Polymer conjugation through an anhydride linkage. This is similar to the previous polymer covalent conjugation however this time it's through an anhydride linkage that is derived from reaction of an acrylic acid co-polymer (I've color coded the co-polymer and the conjugate substituents for clarification) with again the acid chloride of 3-nicotinic acid. This anhydride linkage is also susceptible to hydrolysis *in vivo* to release 3-nicotinic acid. In fact this is the type of linkage used in the polyaspirin polymer of Kathryn Uhrich's, namely the polyanhydride of salicylic acid. Again neutralization of the hydrochloric acid is accomplished by treatment with triethylamine and subsequent washing of the precipitated polyanhydride polymer with water removes the triethylamine hydrochloride byproduct.



3. Entrapment in a polylactic acid polymer. It is widely-known that polylactic acid polyester polymers (PLA) undergo hydrolysis *in vivo* to the lactic acid monomer and this has been exploited as a vehicle for drug delivery systems in humans. Unlike the prior two *covalent* methods where the 3-nicotinic acid is linked by a chemical bond to the polymer, this would be a *non-covalent* method that would encapsulate the 3-nicotinic acid into PLA polymer beads.



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United States
Patent and Trademark Office

2/11/04

Dear Sir,

This enclosed full application claim benefits of my Provisional Patent entitled " Method for treating occlusive vascular diseases & wound healing", application number # 60/446,568 filed on 02/12/03.

Thanks for your support.

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Wynantskill, NY 12198